Papillary cancer nodal surgery and the advisability of prophylactic central neck dissection: Primum, non nocere

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NODAL DISEASE is a centrally important issue for surgeons managing patients with papillary carcinoma of the thyroid (PTC). Cervical lymph node (LN) metastasis may be found in the majority of patients with PTC; the incidence rate varies widely depending on the mode of detection and the definition of node positivity. American Thyroid Association 2009 guidelines note “completeness of surgical resection is an important determinant of outcome... residual metastatic lymph nodes (LN) represent the most common site of disease persistence/recurrence... and adequate surgery is the most important variable influencing prognosis.” Hughes et al, in this issue of Surgery, have provided a retrospective, nonrandomized study of 143 patients with PTC greater than 1 cm, treated surgically over a 7-year period. All patients at the time of presentation lacked clinical evidence of nodal disease (ie, N0 status based on negative physical exam, negative preoperative neck ultrasound, and no lymphadenopathy evident at surgery). The decision to offer prophylactic central neck dissection (pCND) was not made prospectively but was determined by surgeon and patient preference and when applied involved bilateral paratracheal dissection. The 2 retrospective groups (one with and one without pCND during total thyroidectomy) were comparable in terms of tumor size, MACIS score, rates of multifocality, and vascular invasion, though the pCND group had a higher rate of extrathyroidal invasion. Hughes et al found no impact on survival, recurrence or in stimulated thyroglobulin level before and 1 year after radioactive (RAI) treatment. The rate of microscopic nodal disease in clinically N0 central neck was 62%. In patients older than 45 years, pCND upstaged 29% of patients.

MICRO VERSUS MACRO LN METASTASIS

A centrally important but understudied issue in discussion of PTC nodal disease is the distinction between micro and macro (also termed “gross” nodal disease) nodal metastasis. Although most clinicians who actively manage patients with papillary carcinoma are very well aware of the significant differences between these 2 groups, pathologists infrequently, if ever, report this information. Strict clinical definitions segregating micro from macro metastasis have yet to be formulated by multidisciplinary medical endocrine and surgical groups, an increasingly important issue because ultrasonography and other radiographic modalities have significantly lowered the threshold for detection of histologically positive nodes. A preliminary definition of macro (or gross) LN metastasis might include the following basic elements: (a) nodal disease that can be recognized as abnormal or suspicious by preoperative radiographic evaluation; (b) nodal disease that can be routinely recognized as abnormal or suspicious at the time of surgery; (c) nodal disease that both endocrinologist and surgeon, after analysis based on its size, agree can be best treated by surgery as opposed to thyroid hormone, radioactive iodine, or observation.

Macroscopically positive gross nodal disease requiring surgical treatment occurs in approximately 30% of patients with PTC, whereas microscopically positive nodes are far more prevalent. In 80 N0 patients who underwent prophylactic central as well as ipsilateral lateral neck dissections, Quibain et al recently found that the rate of microscopic nodal metastasis was 53% overall (of
which 83% were in the central neck and 17% were in the ipsilateral lateral neck). Similarly, Sywak et al\textsuperscript{5} in 2006 and Hughes et al\textsuperscript{2} found that between 38% and 62% of N0 patients had micro metastasis at pCND.

**LN METASTASIS AND PROGNOSIS**

Traditionally, PTC nodal metastasis has been considered to increase loco-regional recurrence risk, but has been felt to have a weak relationship to overall prognosis. In fact, lymph node status has been omitted from prognostic schemes including AMES, AGES, and MACIS.\textsuperscript{6-13} However, recent studies including a SEER database analysis of nearly 10,000 patients suggest that nodal disease is in fact an important determinant of survival especially in patients over 45 years of age.\textsuperscript{14,15}

Despite the widespread occurrence of microscopically positive nodes in the N0 central neck (38–62% based on recent studies), recurrence in the central neck in N0 patients not treated with pCND occurs rarely, only in 1.3–6% of patients.\textsuperscript{16,17} Ito et al\textsuperscript{18} showed that resection of preoperatively radiographically detected macrometastasis resulted in improved recurrence-free survival, whereas no such prognostic improvement occurred when radiographically negative nodal micrometastasis was resected. Thus microscopic nodal disease in papillary thyroid carcinoma is exceedingly common yet infrequently evolves into clinically significant disease and is of minimal prognostic significance. Clearly, the prognostic importance of nodal disease in papillary thyroid cancers seems centered on detection and treatment of macro LN metastasis.

**NECK NODAL REGIONS AND NECK DISSECTION NOMENCLATURE**

The neck regions typically involved in papillary nodal disease include the lateral neck, which includes regions 2, 3, and 4 (ie, upper, middle, and lower jugular nodes respectively), and the central neck, or region 6. The ATA central neck task force\textsuperscript{19} has recently defined the central neck as being composed of 4 subcompartments: prelaryngeal, pretracheal, and bilateral paratracheal regions. Clinically identifiable nodal disease is treated with compartmental dissection; that is the regions affected by grossly positive nodes are completely dissected rather than individual clinically positive nodes being resected (termed ‘berry picking’). This more comprehensive compartmental philosophy, while not affecting survival, has been shown to reduce nodal recurrence. PTC nodal surgery can typically be divided into central neck dissection (CND), which includes prelaryngeal, pretracheal, and at least 1 paratracheal region, and lateral neck dissection, which typically includes regions 2, 3, and 4 unilaterally.\textsuperscript{19}

A neck dissection (whether central or lateral) is termed therapeutic if performed for preoperatively recognized macroscopic/gross nodal disease. A prophylactic (or elective) neck dissection is performed without the preoperative demonstration of clear macrometastases and is intended to harvest, at best, microscopically positive nodal disease or normal uninvolved nodes.

The ATA recommendations regarding central neck management in their 2006 guidelines were interpreted as encouraging surgeons toward routine pCND in PTC. This prompted significant concern and discussion and as a result, in ATA’s 2009 guidelines,\textsuperscript{1} CND recommendations have been expanded to 3 recommendations (R 27a, 27b, and 27c). These most recent recommendations have been interpreted as indicating a much greater reluctance in performing pCND, describing pCND as an option for advanced tumors and less appropriate for early-stage tumors.\textsuperscript{1} European guidelines suggest that pCND is controversial and is without evidence of clear effect on mortality or recurrence and imply that it may have a role in guiding subsequent treatment and follow-up.\textsuperscript{20}

**PROPHYLACTIC CENTRAL NECK DISSECTION: EFFECT ON SURVIVAL AND /OR RECURRENTCE**

No prospective randomized studies exist regarding the effects of pCND on disease-specific mortality. Tisell et al\textsuperscript{16} found a lower death rate in patients treated with CND compared to previously published patient data from different countries, however no statistical analysis was provided. Similarly, no prospective randomized studies have examined the effect of CND on disease recurrence. Of the 6 retrospective studies looking at this issue, two support lower recurrence rates and four do not.\textsuperscript{17,21-25} There is, therefore, no conclusive published data demonstrating that pCND improves patient survival or disease recurrence.

**PROPHYLACTIC CENTRAL NECK DISSECTION’S ROLE IN UPSTAGING: IS RADIOACTIVE IODINE JUSTIFIED?**

Prophylactic CND, by harvesting microscopically positive nodes in some patients, routinely upstages patients. According to 2010 TNM staging, young patients with microscopically positive nodes harvested at pCND move from N0 to N1a, and
patients over 45 years of age move from stage I to stage III.\textsuperscript{26} Three recent studies suggest that approximately 35\% of patients treated with prophylactic dissection may be so upstaged.\textsuperscript{2,27,28} But what is the clinical significance of such upstaging in the typical low risk patient? Should these microscopically upstaged patients be treated with RAI? Ross et al,\textsuperscript{29} in a recent large retrospective analysis of papillary microcarcinomas, found that RAI did not decrease recurrence rates in patients with nodal metastasis. Similarly, among over 1100 low-risk patients with MACIS scores <6, Hay\textsuperscript{30} found that RAI treatment did not affect mortality or recurrence in node-positive patients. Current ATA guidelines suggest that RAI ablation for patients with nodal disease does not impact on survival and suggest that there is conflicting data regarding its impact on recurrence in patients less than 45 years old, and so it should be used selectively in reducing recurrence in patients over 45 years of age.\textsuperscript{1} One may, therefore, question the utility of RAI in patients microscopically upstaged by pCND. If, on the other hand, the pCND node harvest is negative then RAI can be withheld from patients who would have not been offered it in the first place. The argument for pCND as a staging tool has lost its traction. Bonnet et al\textsuperscript{31} reported recently, based on retrospective data, that aggressive pCND resulted in increased use of RAI and, ultimately, in favorable outcomes. However, it is possible that controlled prospective studies might achieve similarly favorable results without pCND and additional RAI treatment based on such “microscopic upstaging.” We must be aware that diagnostic procedures allowing preclinical disease identification may provide statistical artifact that can support therapeutic benefit. In analysis of lung cancer patients Feinstein found new diagnostic imaging procedures led to false over estimation of survival in patient cohorts without change in individual patients outcomes. Though “lead time” bias a given patient’s survival may appear enhanced without necessarily prolonging the duration of that patient’s life through earlier preclinical detection of disease and has been termed the “Will Rogers phenomenon.” Prophylactic central neck dissections provide for microscopic upstaging of through detection of preclinical disease.\textsuperscript{32}

**PROPHYLACTIC CENTRAL NECK DISSECTION AND THYROGLOBULIN**

The initial work of Sywak et al\textsuperscript{5} suggested that unilateral pCND (ie, ipsilateral paratracheal dissection) was associated with a lower thyroglobulin postoperatively. However, Hughes et al\textsuperscript{2} fail to demonstrate decreased thyroglobulin levels in patients who underwent bilateral central neck dissection at the time of thyroidectomy. The use of thyroglobulin as a surgical outcome measure (as opposed to more typical outcome metrics for cancer treatment, survival, and recurrence) is problematic. Thyroglobulin levels vary with assay type,\textsuperscript{33} may be affected by antithyroglobulin antibodies, and may vary relative to residual thyroid tissue. If serum thyroglobulin is judged to be an important surgical outcome metric, pCND has now been shown to offer no benefit in terms of lower postoperative thyroglobulin. Perhaps the next step in the pursuit of low postoperative thyroglobulin is the addition of prophylactic bilateral lateral neck dissections to in all PTC patients?

**MORBIDITY OF PROPHYLACTIC CENTRAL NECK DISSECTION**

Hughes et al\textsuperscript{2} state that central compartment lymph node dissections can be performed safely. The Hughes study is notable for recurrent laryngeal nerve (RLN) paralysis rate of 3\% in his total thyroidectomy group. In the Hughes study, cases of RLN injury were confirmed by laryngoscopy, implying that laryngoscopy was performed only in symptomatic postoperative patients. Such a selective approach to postoperative RLN quality assessment significantly underestimates RLN paralysis rates.\textsuperscript{34} The true rate of RLN paralysis is typically twice the observed rate with such selective laryngoscopy algorithms.\textsuperscript{34}

The safety of prophylactic lymph node dissection is very much in question even in expert hands. Mazzaferri et al,\textsuperscript{35} in reviewing issues relating to pCND, notes that most studies show a clear increase in recurrent laryngeal nerve injury when CND is added to total thyroidectomy. All reviewed studies showed higher rates of transient hypoparathyroidism with the addition of CND.\textsuperscript{35} A fundamental guiding rule to be aware of is that as more surgery is performed, more complications arise. It should also be noted that not all surgeons performing thyroidectomy perform it routinely: one half of thyroid surgeries in the US are performed by surgeons who perform 5 or fewer thyroid surgeries annually.\textsuperscript{36} Additional training in thyroid surgery in surgical residency programs may provide a long-term solution to this problem, but at present in some regions of the US sufficient surgical experience for routine node dissection may not always be available locally.

Even if prophylactic node dissection can be done safely, it does not follow that it should be done. The work of Sywak et al\textsuperscript{5} and Hughes\textsuperscript{2} suggest that only a
small fraction of patients will eventually require therapeutic central neck dissection if prophylactic nodal dissection is not performed. Instead of doing unfocused prophylactic bilateral paratracheal dissections in all patients presenting with PTC, one may offer focused surgery only to those rare patients who actually develop macroscopic nodal recurrence in the central neck. This focused surgery would involve only the affected unilateral paratracheal region which has great airway and parathyroid safety implications. Shen et al. have recently shown the risk of such focused unilateral revision central neck surgery is no higher than first-time central neck surgery. The smaller number of cases requiring this focused revision surgery could be handled by regional centers of excellence.

MICROSCOPIC NODAL DISEASE OR EXTRATHYROIDAL DISEASE: WHAT IS OUR FOCUS?

For a thyroid surgeon clinician, of the many existing day-to-day management problems in treatment of low and high risk patients with papillary carcinoma, difficulty in management of subclinical microscopic nodal disease is, frankly, not on the top of list. Recognition and appropriate treatment of extrathyroidal disease on the other hand does have tremendously meaningful impact on PTC prognosis. Extrathyroidal extension (ETE) ranges from 4% to 16% in patients with PTC. Preoperative recognition of ETE of disease can be obtained from laryngoscopy. The importance of ETE essentially normalized and became equivalent to patients without ETE. The presence of surgical skill essential for a surgical procedure. Given the tremendously favorable prognosis of most patients with papillary thyroid cancer with survival for the vast majority of patients being excellent, we need to carefully weigh any additional intervention, especially one associated with morbidity. We should generally endeavor to perform less, not more, surgery. There are many dissections that can be performed; but without any additional survival, recurrence, or thyroglobulin benefit, pCND is a dissection not worth doing.

In conclusion, due to the lack of significance of pCND’s impact on the reasonable clinical outcome measures of survival and recurrence investigators committed to pCND have expanded their search to include postoperative thyroglobulin measures and have demonstrated lack of benefit even in this nonstandard surgical outcome measure. They demonstrate that the microscopic upstaging of patients does impact on RAI treatment decisions made by their nuclear medicine and endocrinology colleagues.

The time-tested surgical principle of resection of gross disease in management of patients with PTC will serve us well. Additional efforts should be focused on appropriate initial recognition of macroscopic nodal disease preoperatively and on its initial adequate treatment. Microscopic disease is not a rational surgical target in PTC. Nodal surgery disease in typical low-risk papillary carcinoma patients should be based on preoperative objective radiographic evaluation, and should target macro rather than micro nodal metastasis. Surgical treatment like any other treatment should be titrated to the specific risk of the individual patient with differentiated thyroid cancer.

The REFERENCES

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